Genomic analysis suggests that mRNA destabilization by the microprocessor is specialized for the auto-regulation of Dgcr8.

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Public Summary:
MicroRNAs are short RNA molecules that do not encode for proteins but rather regulate the production of proteins from messenger RNAs. Importantly, microRNAs have been implicated in a broad range of stem cell roles in both healthy and diseased tissues. MicroRNAs show great promise as both biomarkers and therapeutics for disease. The global levels of microRNAs in any one cell can dramatically alter the properties of the cell. For example, it has been shown in a number of cancers, microRNAs are globally down and this downregulation is functionally linked to tumor progression. Therefore, regulating the overall production of microRNAs is a central feature in how the cell will behave. Here, we describe a feedback loop that tightly regulates global levels of microRNAs in a cell. Building on a previous publication of ours, we show that the feedback loop is unique to a single target that is intimately involved in maintaining global microRNA homeostasis.

Scientific Abstract:
BACKGROUND: The Microprocessor, containing the RNA binding protein Dgcr8 and RNase III enzyme Drosha, is responsible for processing primary microRNAs to precursor microRNAs. The Microprocessor regulates its own levels by cleaving hairpins in the 5'UTR and coding region of the Dgcr8 mRNA, thereby destabilizing the mature transcript. METHODOLOGY/PRINCIPAL FINDINGS: To determine whether the Microprocessor has a broader role in directly regulating other coding mRNA levels, we integrated results from expression profiling and ultra high-throughput deep sequencing of small RNAs. Expression analysis of mRNAs in wild-type, Dgcr8 knockout, and Dicer knockout mouse embryonic stem (ES) cells uncovered mRNAs that were specifically upregulated in the Dgcr8 null background. A number of these transcripts had evolutionarily conserved predicted hairpin targets for the Microprocessor. However, analysis of deep sequencing data of 18 to 200nt small RNAs in mouse ES, HeLa, and HepG2 indicates that exonic sequence reads that map in a pattern consistent with Microprocessor activity are unique to Dgcr8. CONCLUSION/SIGNIFICANCE: We conclude that the Microprocessor's role in directly destabilizing coding mRNAs is likely specifically targeted to Dgcr8 itself, suggesting a specialized cellular mechanism for gene auto-regulation.